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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/918,537	08/22/1997	KOICHI AKASHI	LSJU-64PAT	6190

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/918,537	AKASHI ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 19-22* _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 1997* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 12/10/03 have been entered. Claims 1 and 7 have been amended, and claims 19-22 are newly submitted. Claims 1-11 and 19-22 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the response and amendment will not be reiterated.

Claim Objections

Claims 1, 7, and 19 are objected to because a comma should be inserted after "B cells".

Claim 7 is objected to because of the symbol after "IL-7R" in line 6 should be "alpha".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolating/obtaining a *bipotent* mammalian common lymphoid progenitor cell that is capable of giving rise to each of T cells and B cells, does not reasonably provide enablement for isolating/obtaining a

multipotent mammalian common lymphoid progenitor cell that is capable of giving rise to each of T cells, B cells, and *NK cells*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Amended claims 1 and new claim 19 are drawn to "an individual progenitor cell in said composition is capable of giving rise to each of T cells, B cells and natural killer cells". The disclosure as originally filed teaches using a single cell from Lin^-, $Thy\text{-}1^-$, $IL\text{-}7R\alpha^+$, and $C\text{-}kit^{low}$ cell population to give rise to B and T lymphocytes, and states, "the subject CLP population has prominent T, B, and NK cell-restricted reconstitution potential, and can give rise to at least both T and B cells" (specification, page 21, lines 1-2). The original disclosure does not teach that the single cell could also give rise to NK cells. In view of applicants' argument concerning the uncertainty of the presence of a multipotent common progenitor cell and supporting evidence from *Shortman et al*, it appears necessary that the specification provides sufficient support commensurate with the full scope of the claims.

It is necessary that applicants provides support that is reduced to practice for what is claimed now because applicants have argued and provided reference showing that the skilled artisan remains in doubt concerning whether it is one multipotent progenitor cell or a mixture of unipotent progenitor cells that give rise to B-, T-, and NK cells. Accordingly, it is critical that the specification provides sufficient support when claiming that it is a multipotent but not a mixture of unipotent progenitor(s) that give rise to all three types of lymphoid lineage cells.

It is also necessary for applicants to provide support for claimed markers recited in claims 5 and 22, because the specification only prophetically teach that these markers could be used for identifying the common lymphoid progenitor cells. Although these markers are known in the art to identify certain unipotent progenitors, neither the art of record nor the specification confirms that they are expressed in a multipotent common lymphoid progenitor cell as claimed.

Furthermore, *Maki et al* (PNAS 1996;93:7172-7) teach that IL-7 receptor-deficient mice lacks $\gamma\delta$ T cells, and have reduced numbers of $\alpha\beta$ T cell and B cells, but normal development of NK cells. Thus, it appears NK cell progenitors may be distinct to T and B progenitors in certain aspect, at the least. Accordingly, it appears reasonable to cast doubt as to whether the very progenitor cell that gives rise to T- and B-cells would also give rise to NK cells, and it appears appropriate to require that applicants provide an adequate support commensurate to the scope with what is now claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claims 1 and 7 recite "an individual progenitor cell in said composition is capable of giving rise to each of T cells, B cells and natural killer cells", here the individual progenitor cell is not limited by the surface markers recited in the

same claim, and the individual progenitor cell could be the 5% cells of the composition that do not bear the recited surface markers. Accordingly, the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, and 6-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Olweus et al* (US 6,555,324), in view of *Galy* (US 5,972,627), and the rejection applies to new claims 19 and 20.

As indicated in the previous Office action, *Olweus et al* teach that progenitor cells committed to lymphoid lineage can be identified with markers of CD34 and CD38, plus IL-7 receptor (i.e. CD34+, CD38+, IL-7R+, column 2, lines 36-61). Although *Olweus et al* do not specifically teach the c-kit and lin markers for these cells, these limitations are taught by *Galy et al*. *Galy et al* teach that human T, B, and NK cells (cells of lymphoid lineage) arise from a common bone marrow progenitor subset, which are characterized by surface markers as CD34+, CD38+, CD45+, Lin^-, $Thy\text{-}1^-$, and $C\text{-}kit^{lo}$ (See e.g. § bridging pages 459-60, fig. 1, middle and right panel, and column 16, lines 33-42), and which would not give rise to myeloid cells (abstract). *Galy* does not teach IL-7 receptor

alpha, however, the teaching of *Olweus et al* has shown that it is known in the art that IL-7R is a critical marker for identifying lymphoid progenitor cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Olweus et al* and *Galy et al,* by including the IL-7R marker as taught by *Olweus et al* with the set of markers as taught by *Galy* for identifying and enriching cells from lymphoid progenitor subset with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to combine the methods because the additional marker (IL-7R) may enhance the isolation/enrichment process, thus, obtaining enriched lymphoid progenitor cells. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The amended and new claims 19-20 are drawn to a single hematopoietic cell characterized by IL-7RA+, CD45+, Lin^-, $Thy\text{-}1^-$, and $C\text{-}kit^{low}$ and capable of giving rise to each and every T, B, and NK cells. In 12/10/03 response, applicants argue that neither one of the cited references demonstrates the existence of a single common lymphocyte progenitor cell which gives rise to any of B-, T-, or NK cells, and further cites *Shortman et al*, who suggests that a clonal study should be conducted to eliminate the possibility that the population is a mix of individual unipotent progenitors with identical surface phenotype. Applicants further argue that Olweuse et al fail to cure the shortcoming of Galy (Remark, pages 5-6).

The arguments and cited reference have been fully considered but they are not sufficient to overcome the rejection for reasons of record and following.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, as reiterated above, it is the combined teaching of Olweus et al and Galy et al that arrive at the claimed invention. Moreover, *Galy et al* appears to teach not only a common progenitor subset (e.g. the title), but also a multipotent common progenitor cell. For example, *Galy et al* state, "THE EXISTENCE OF A COMMEN PRECURSOR FOR LYMPHOID CELLS IN BONE MARROW HAD BEEN SUGGESTED FOR YEARS", and "WE SPECULATE THAT A COMMON CLONE FOR ALL LYMPHOID CELLS AND DCS EXISTS AND MIGHT BE FOUND WITHIN THE CD34+ LIN- CD10+ BONE MARROW POPULATION" (1st paragraph, Discussion), although they acknowledge that multi-lineage clonal assays are need to confirm the existence of such cell. Here, the clonal study disclosed in the specification has been suggested by both *Galy et al* and *Shortman et al* (as pointed out by applicants), and the results only confirms the speculation of *Galy et al*, there is no surprise finding presented. *Shortman* reference raise the remain issue regarding the existence of a common progenitor cell for T, B, and NK cells, and indicates the needs for further confirmation, but it does not provide evidence to the contrary. Second, *Shortman* reference confirms that even if the hematopoietic subset is comprised of a mixture of unipotent progenitor cells, they bear identical surface markers. This leads to the third reason why the argument is insufficient, i.e. the

claimed multipotent common progenitor cell as recited is identified by the surface markers, thus, as long as the combined teachings reasonably taught identifying a lymphoid progenitor cell with the recited markers, they met claim limitation, i.e. the cell population identified would comprise the multipotent common progenitors. Moreover, It is noteworthy that *Shortman et al* discuss the instantly cited Galy's finding and the importance of IL-7 (that needs of IL-7R to function) in lymphoid lineage development (page 41), this further illustrates the levels of reasonably skilled in the art, and it would have been obvious to combine the markers of *Galy et al* with that of *Olweus et al* for identifying the common lymphoid progenitor cells. Accordingly, the rejection stands.

The prior rejection of claims 1-4, and 6-11 under 35 U.S.C. 103(a) as being unpatentable over *Olweus et al* (US 6,555,324), and *Galy* (US 5,972,627) as applied to claims 1-3 and 6-10 above, further in view of *Kawamoto et al* (Int Immunol 1997 July;9:1011-1019) is withdrawn in view of amendment and arguments that *Kawamoto et al* do not identify a Sca-1^{lo} population, and considering *Kawamoto et al* teach Sca-1 in the context of a cell population defined as c-kit+ population which also give rise to myeloid cells, and no bipotent T and B progenitor cells were detected.

The prior rejection of claims 1-3, and 5-10 under 35 U.S.C. 103(a) as being unpatentable over *Olweus et al* (US 6,555,324), and *Galy* (US 5,972,627) as applied to claims 1-3 and 6-10 above, further in view of *Kincade et al* and *Ballas et al* (J Immunol

1990;145:1039-45) is withdrawn in view of amendment and arguments that *Kincade et al and Ballas et al* describe certain cell surface markers in a unipotent precursor, and do not teach all the recited markers in the context of the common lymphoid progenitors.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730.

The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
March 7, 2004